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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/722,379	11/24/2003	Natalya Rapoport	T5986.PCT.US.B	4634

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EXAMINER	
KARPINSKI, LUKE E	
ART UNIT	PAPER NUMBER
1616	
MAIL DATE	DELIVERY MODE
09/12/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/722,379	RAPOPORT, NATALYA	
	Examiner	Art Unit	
	LUKE E. KARPINSKI	1616	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 May 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-20* is/are pending in the application.

4a) Of the above claim(s) *2,4,6,8 and 13-17* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 3, 5, 7, 9-12, and 18-20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Receipt of Arguments/Remarks filed 5/23/2008 is acknowledged.

Claims

Claims 1-20 are currently pending and under consideration.

Claims 2, 4, 6, 8, and 13-17 are withdrawn as being drawn to non-elected subject matter.

Claims 1, 3, 5, 7, 9-12, and 18-20 are under consideration in this action.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Applicant Claims
2. Determining the scope and contents of the prior art.
3. Ascertaining the differences between the prior art and the claims at issue, and resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

1. Claims 1, 3, 5, 7, 9-11, and 18-20 are rejected under 35 U.S.C. 103(a) as being unpatentable over US Patent No. 5,827,533 to Needham in view of US Patent No. 6,353,055 B1 to Kabanov et al. and US Patent No. 5,830,430 to Unger et al.

Applicant Claims

Applicant claims a method for delivery of a hydrophobic drug to a selected site comprising administering a composition comprising a micellar drug carrier with a hydrophobic core and a hydrophobic drug, wherein said micelle drug carrier is a member selected from ABA-triblock copolymers or a mixture of said copolymers and Peg-ylated phospholipids. Said method also comprises applying ultrasound at 20-100 kilohertz to effect drug release form the carrier. The Applicant also claims specific monomers for the polymer and specific drugs.

Determination of the Scope and Content of the Prior Art (MPEP §2141.01)

Needham teaches methods for delivery of a hydrophobic drug (col. 17, lines 3-5), delivery to a selected site in a patient (col. 21, lines 2-7), a micellular drug carrier (col. 5, line 66 to col. 6, line 5), a hydrophobic core (col. 9, line 64 to col. 10, line 6), PEG-ylated lipids (col. 9, lines 26-52), and the utilization of poly (propylene oxide) –poly (ethylene oxide) diblock copolymers as micelle forming surfactants in combination with the liposome membrane (col. 24, lines 3-13), as claimed in claim 1.

Ascertainment of the Difference between Scope the Prior Art and the Claims (MPEP §2141.012)

Needham does not teach an ABA triblock copolymer of poly (ethylene oxide) – poly (propylene oxide) –poly (ethylene oxide) hereafter referred to as (PEO PPO PEO) or (ABA), as claimed in claim 1. This deficiency in Needham is cured by Kabanov et al. Kabanov et al. teach ABA triblock copolymers (col. 3, line 18), a PEO PPO PEO triblock copolymer (col. 11, lines 1-10, structure XIV), as well as the fact that both diblock and triblock copolymers are useful for delivery of an active to cells (col. 3, lines 26-31).

Further, Needham does not teach applying ultrasound to release drug from the micelle carrier as claimed in claim 1. This deficiency is cured by Unger et al. Unger et al. teach micelle structures for delivery of a bioactive agent (abstract), the use of ultrasound to effect release of the bioactive agent for cellular uptake at a specified site (col. 27, line 51 to col. 28, line31), and a range of 0.25 to 100 megahertz (col. 28, lines 60-61).

Finding of Prima Facie Obviousness Rational and Motivation

(MPEP §2142-2143)

Regarding claim 1, it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to practice the methods of Needham with an ABA triblock copolymer, as taught by Kabanov et al. in order to produce the invention of instant claim 1.

One of ordinary skill in the art would have been motivated to do this because Needham teaches the use of micelle structures comprising diblock copolymers and Kabanov et al. teach that diblock and triblock copolymers can both be used in the formation of micellar structures. It is common in the art for one of ordinary skill in the art to substitute one functional equivalent for another. . Therefore it would have been obvious to utilize the ABA triblock copolymer, of Kabonov et al., in the compositions of Needham.

Further regarding claim 1, it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to practice the methods of Needham and rupture the micelles with ultrasound, as taught by Unger et al. in order to produce the invention of instant claim 1.

One of ordinary skill in the art would have been motivated to do this because Needham teaches the use of micelle structures to deliver drugs to a selected site in a patient and Unger et al. teach the use of ultrasound to rupture micelle structures and effect delivery of a bioactive agent. Unger et al. teaches that this is useful in delivery and controlled release of a bioactive agent to targeted tissue. The ultrasound can be

used to release a desired amount of the bioactive agent to the specific site, while the agent remains within the micelle at other sites in the body, thereby minimizing any negative effects of the agent. Therefore it would have been obvious to utilize ultrasound to rupture micelles, as taught by Unger et al., in the methods of Needham.

Further regarding claim 1, it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to practice the methods of Needham and utilize 20-100 kilohertz to rupture said micelles, as taught by Unger et al. in order to produce the invention of instant claim 1.

One of ordinary skill in the art would have been motivated to do this because Unger et al. teaches using a range of .25 to 100 megahertz. It was well within the capabilities of one of ordinary skill in the art at the time of the invention to determine an optimum frequency at which the micelles rupture.

From the teachings of the reference, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

1. **1. Claim 12 is rejected under 35 U.S.C. 103(a)** as being unpatentable over US Patent No. 5,827,533 to Needham in view of US Patent No. 6,353,055 B1 to Kabanov et al. and US Patent No. 5,830,430 to Unger et al., as applied to claim 1 above, in further view of US Patent No. 4,332,934 to Emanuel et al.

Applicant Claims

Applicant claims the hydrophobic drug as ruboxyl.

Determination of the Scope and Content of the Prior Art (MPEP §2141.01)

The teachings of Needham, Kabanov et al., and Unger et al. are delineated above. Further taught by Needham is the utilization of daunorubicin (col. 17, lines 3-5).

Ascertainment of the Difference between Scope the Prior Art and the Claims (MPEP §2141.012)

None of Needham, Kabanov et al., or Unger et al. teach ruboxyl as claimed in claim 12. This deficiency in Needham, Kabanov et al., or Unger et al. is cured by Emanuel et al. Emanuel et al. teach ruboxyl as a less toxic derivative of daunorubicin with higher anti-tumor activity (abstract). It is noted that rubomycin is commonly referred to as daunorubicin (col. 1, lines 23-25).

Finding of Prima Facie Obviousness Rational and Motivation

(MPEP §2142-2143)

Regarding claim 12, it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to produce the combined compositions of Needham and Kabanov et al. with ruboxyl, as taught by Emanuel et al. in order to produce the invention of instant claim 12.

One of ordinary skill in the art would have been motivated to do this because Needham teaches the utilization of daunorubicin and Emanuel et al. teach that ruboxyl is a less toxic and more active derivative of daunorubicin. Therefore it would have been

obvious to utilize the ruboxyl of Emanuel et al., with the combined compositions of Needham and Kabanov et al. in order to produce a less toxic and more active formulation.

From the teachings of the reference, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1 and 3 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 22 of U.S. Patent No. 6,649,702 to Rapoport et al. in view of Kabanov et al. and Unger et al.

Determination of the Scope and Content of the Prior Art (MPEP §2141.01)

The teachings of Kabanov et al. and Unger et al. are delineated above.

Rapoport et al. claim a method for administering a hydrophobic drug to a patient comprising administering block polymer micelles which contain said drug in a hydrophobic core and applying ultrasound to release said drug.

Ascertainment of the Difference Between Scope the Prior Art and the Claims

(MPEP §2141.012)

Rapoport et al. do not expressly disclose a triblock copolymer. This deficiency in Rapoport et al. is cured by the teachings of Kabanov et al.

Rapoport et al. also do not expressly disclose an ultrasound frequency of 20-100 kilohertz to release the drug from the carrier. This deficiency in Rapoport et al. is cured by the teachings of Unger et al.

Finding of Prima Facie Obviousness Rational and Motivation

(MPEP §2142-2143)

1. It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to use the triblock copolymer in the compositions of Rapoport et al., as taught by Kabanov et al., and produce the instant invention.

One of ordinary skill in the art would have been motivated to do this because Rapoport et al. teaches the use of micelle structures comprising block copolymers and Kabanov et al. teach that diblock and triblock copolymers can both be used in the formation of micellar structures. .

2. It would have been obvious to one of ordinary skill in the art at the time the invention was made to use a frequency of 20-100 kilohertz in the method of Rapoport et al. as taught by Unger et al. and practice the instant method.

One of ordinary skill in the art would have been motivated to do this because Unger et al. teaches using a range of .25 to 100 megahertz. It was well within the capabilities of one of ordinary skill in the art at the time of the invention to determine an optimum frequency at which the micelles rupture.

From the teachings of the reference, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Response to Arguments

Applicant's arguments filed 5/23/2008 have been fully considered but they are not persuasive.

Applicant argues that the references fail to disclose or teach an ultrasound frequency of 20-100 kHz and that Unger et al. teach away from the utilization of such low frequencies.

This argument is not found persuasive. Although Unger et al. teach a low end frequency of 250mHz and applicant claims 100 mHz as their high end, the claimed range would still be obvious over the combination of references. Unger et al. is relied upon to teach that, in general, it is known to rupture micelles through the utilization of ultrasound, as well as for a range of frequencies which are known to be capable of rupturing the specific micelles taught by Unger et al. One of ordinary skill in the art would have readily seen that different micelles would rupture with different ranges of frequencies and that what may work for one micelle may not work for another. To determine the optimum frequency for a specific micelle would have required routine and simple experimentation and it would be expected that a broad range of frequencies would be tried, including 20-100 kHz.

In regards to the statement that Unger teaches away from the instant invention. This is also not persuasive. Although Unger et al. teach that higher frequencies absorb into smaller vesicular species better this is not mean that lower frequencies do not also rupture said species. Unger also teaches that higher frequencies cannot penetrate very deep into the skin which means that for deeper penetration one would utilize a lower

frequency. Further, applicant does not claim any particular particle size, so any discussion directed to molecule size is not persuasive.

For these reasons the utilization of 20-100 kHz would have been obvious to one of ordinary skill in the art at the time of the invention.

Applicant also argues that the methods of Unger et al. require the utilization of gases.

This argument is not found persuasive because Unger simply teaches that one embodiment may incorporate the utilization of gases but they are not required.

Applicant also argues that their disclosure discloses micelles of a particular size and according to the teachings of Unger et al. an optimal energy of 30-105 mHz would be utilized to rupture said micelles.

This argument is not found persuasive because applicants have no claims directed to a micelle size.

Applicant also argues that Needham teaches that micelles are not useful for drug administration when delayed administration is desired.

This argument is not found persuasive for two reasons. The first is that there is no claim directed to delayed administration. The second is the fact that Needham teaches formulating liposomes to contain actives for extended periods of time without loss of membrane stability, this would read on delayed administration.

Applicant also argues that references must be considered as a whole, including disclosures that teach away from making the invention.

This argument is not found persuasive because, as applicant's arguments of the references teaching away are answered above, there is no teaching away from the instant invention in any of the cited references, and therefore no picking and choosing was done.

Applicant also argues that due to not considering the disclosures of teaching away that the rejection was formulated by picking and choosing and that hindsight reconstruction was also utilized to formulate the rejection.

Due to the fact that the examiner has answered the teaching away arguments, there are no grounds to argue that any picking and choosing or hindsight reconstruction was utilized in the formulation of the rejection.

The applicant also argues that it is believed that the instant invention has solved a long felt need and therefore the invention cannot be obvious.

This argument is not found persuasive because the long felt need of rupturing micelles carrying drugs has already been filled by Unger et al. The instant invention simple utilizes a different block copolymer, and therefore requires a different ultrasound frequency, all of which is rendered obvious by the combined disclosures of Needham, Unger et al., and Kabanov et al..

The applicant finally argues that claim 12 is also improperly rejected due to the fact that claim 12 is dependant upon claim 1 and points out the reasons for improper rejection as applied to claim 1.

This argument is not found persuasive because none of applicant's arguments, in regard to claim 1, have been found persuasive.

Regarding the double patenting rejection, applicant argues that Unger et al. does not cure the deficiency of the ultrasound frequency.

These arguments are not found persuasive because Unger et al. is utilized for the general teaching of utilizing ultrasound and for an example of frequencies which are capable of rupturing a micelle. Further, the disclosure of Rapoport et al. claims subjecting a region of the body to pulsed ultrasound in order to release said drug (claim 22), a genus of ultrasound frequencies has been claimed in Rapoport and the instant invention simply claims a species of said genus, which would be obvious to utilizes in light of Rapoport's claim to all ultrasound frequencies.

Conclusion

Claims 2, 4, 6, 8, and 13-17 are withdrawn as being drawn to non-elected subject matter.

Claims 1, 3, 5, 7, 9-12, and 18-20 are rejected.

No claims are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the

shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Inquiries

Any inquiry concerning this communication or earlier communications from the examiner should be directed to LUKE E. KARPINSKI whose telephone number is (571)270-3501. The examiner can normally be reached on Monday Thursday 9-4 EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Johann R. Richter can be reached on 571-272-0646. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

LEK

/Mina Haghighatian/
Primary Examiner, Art Unit 1616